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Review

Neuropsychiatric systemic lupus erythematosus and cognitive dysfunction: The MRL-*lpr* mouse strain as a model

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ABSTRACT

Mouse models of autoimmunity, such as (NZB × NZW)F1, MRL/MpJ-Fas^{lpr} (MRL-*lpr*) and BXSB mice, spontaneously develop systemic lupus erythematosus (SLE)-like syndromes with heterogeneity and complexity that characterize human SLE. Despite their inherent limitations, such models have highly contributed to our current understanding of the pathogenesis of SLE as they provide powerful tools to approach the human disease at the genetic, cellular, molecular and environmental levels. They also allow novel treatment strategies to be evaluated in a complex integrated system, a favorable context knowing that very few murine models that adequately mimic human autoimmune diseases exist. As we move forward with more efficient medications to treat lupus patients, certain forms of the disease that requires to be better understood at the mechanistic level emerge. This is the case of neuropsychiatric (NP) events that affect 50–60% at SLE onset or within the first year after SLE diagnosis. Intense research performed at deciphering NP features in lupus mouse models has been undertaken. It is central to develop the first lead molecules aimed at specifically treating NPSLE. Here we discuss how mouse models, and most particularly MRL-*lpr* female mice, can be used for studying the pathogenesis of NPSLE in an animal setting, what are the NP symptoms that develop, and how they compare with human SLE, and, with a critical view, what are the neurobehavioral tests that are pertinent for evaluating the degree of altered functions and the progresses resulting from potentially active therapeutics.

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Abbreviations: cAMP, cyclic adenosine monophosphate; CBA/J, C.C.x Bagg, strain A/Jackson; MRL, Murphy Roths Large; PDE, phosphodiesterase; Ab, antibody; CSF, cerebrospinal fluid; lpr, lymphoproliferation; NP, neuropsychiatric; SLE, systemic lupus erythematosus.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem relapsing–remitting autoimmune disease, primarily affecting females [1], which can be influenced by hormonal, genetic and environmental factors [2–7]. Clinical studies have shown that neurologic and neuropsychiatric (NP) symptoms occur in up to 75% of patients, a condition representing a particularly severe form of the disease known as NPSLE [8]. Some of the most frequent NP symptoms, of unknown etiology, are cognitive deficits (e.g. mood and anxiety disorders, memory impairment) [9]. Diagnosis of NPSLE remains essentially clinically defined and requires interpretation of complex criteria developed by the American College of Rheumatology (ACR), as no single laboratory test or imaging is sufficiently sensitive and specific to be diagnostic [10,11]. NP manifestations seem not to be correlated with lupus flares [12], further confounding diagnosis and emphasizing the necessity to rule out other potential etiologies such as medication-induced (corticosteroid) psychiatric symptoms, infections, or metabolic abnormalities [13,14] to establish a possible diagnosis. While lupus patients with long duration of disease hold concurrently several factors that may provoke NP manifestations, affective, cognitive and mood disorders can be found in patients with newly diagnosed disease [15]. Disruption of blood brain barrier (BBB), brain pathology, and the presence of auto-antibodies (autoAbs) are central components of NPSLE.

The lack of insight onto pathogenic mechanisms has required the development of animal models. In a special breed of lupus-prone mice, the MRL/MPJ-Fas^{lpr} (thereafter named MRL-*lpr*) substrain, the onset of systemic autoimmunity and inflammation is accompanied by various deficits in brain function comparable to that observed in SLE patients, providing a useful model to study NPSLE. Interestingly, NP manifestations can also appear early in these mice and are primarily driven by autoimmune process [16]. This review will focus on the validity of the MRL model in relation with cognition, and a particular emphasis is given to consideration of these mice as a model of choice to evaluate potential neuroprotective drugs. As regards other spontaneous models of SLE, the reader will find specific information in comprehensive reviews published elsewhere [17,18].

2. NPSLE: CNS involvement in human SLE

The manifestations of NPSLE are variable and can cover the whole spectrum of psychiatric dysfunction. Patients can experience diffuse, or focal central nervous system (CNS) disorders, as well as peripheral nervous system troubles (Table 1) [9,19–21]. These NP manifestations are not all at the same degree of severity, and are often difficult to distinguish from other conditions and etiologies.

As most NP events (50–60%) occur at SLE onset or within the first year after disease diagnosis, the NPSLE phenotype may be a presenting feature of lupus, constituting the initial patient presentation [10]. However, NPSLE phenotype may also occur outside the context of a SLE flare [22]. When compiling published data, a great variability in reported NPSLE prevalence is usually found (15–75%) [8,19,23,24]. This discrepancy results from many factors such as study design (prospective/retrospective), laboratory methodologies, lack of accepted consensus for diagnosis, selection criteria of patients [e.g. ethnic, demographic, clinical differences (disease duration and activity, duration of follow-up)], rarity of some NP syndromes, or variability in the sensitivity of diagnostic tests assessing behavioral dysfunction [23,25]. Concerning morbidity and mortality, NPSLE is associated with increased global SLE disease activity, poorer prognosis and earlier mortality [26–28]. Recently, a study conducted on a large cohort of carefully phenotyped NPSLE investigated the causes of death and the characteristics associated with mortality [29]. A 10-fold increase mortality rate was reported in this group of patients, the most common causes of death being infections and NPSLE itself.

More than 20 pathogenic brain-reactive autoAbs have been associated to NPSLE [30]. AutoAbs and cytokines found in the serum and cerebrospinal fluid (CSF) of patients have been proposed as important factors in the etiology of CNS damage [31–36]. Furthermore, a disruption of the BBB's integrity, allowing diffusion of proteins and small molecules such as

Table 1

Neuropsychiatric syndromes associated with SLE¹, as defined by ACR nomenclature [9].

Central nervous system	
Diffuse neurological manifestations	Focal neurological manifestations
Acute confusional state	Aseptic meningitis
Psychosis	Cerebrovascular disease
Depression	Seizures
Mood disorders	Movement disorder
Anxiety disorders	Myelopathy
Cognitive dysfunction	Demyelinating syndrome
Headache ²	
Peripheral nervous system	
Cranial neuropathy	
Autonomic neuropathy	
Mononeuropathy single/multiplex)	
Myasthenia gravis	
Plexopathy	
Polyneuropathy	
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)	

¹ Abbreviations: ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.

² Association with SLE is still the subject of intense debates [179–181].

immunoglobulins (Igs) and cytokines into the CSF, is now considered as an important component in NPSLE development [37–39]. Increased CSF levels of Igs, Abs and proinflammatory cytokines, as well as elevated albumin concentration, are indicative of increased BBB's permeability [40–42], and have additionally been associated with NP manifestations [40,43–47].

Neuroimaging plays a substantial role in detecting neurological abnormalities in SLE patients [48–54]. Magnetic resonance imaging (MRI) is generally used but may occasionally fail in NPSLE. As an illustration, more than 40% of NPSLE patients show normal MRI scans [14,55] and even if brain imaging reveals abnormalities (e.g. cerebral atrophy, subcortical white matter lesions, regional neurometabolic dysfunctions, hypoperfusion), these findings are often nonspecific, some of them being also observed in patients without NP manifestations and in the general population after mid-adult life [55–58]. Brain atrophy, which is however quite often reported [48] has been proposed to reflect progressive neuronal injury and demyelination. Altogether, data reported so far suggest the existence of strong links between neuronal cell death, abnormal autoimmune functioning and NP manifestations [59].

Cognitive impairments and emotional disturbances are frequent in NPSLE. However, whether such dysfunctions in memory and affects are inherent to SLE or secondary (epiphenomena), resulting from infection, corticosteroid treatment, or hormonal/metabolic dysfunction, for example, remains unclear.

Studying NPSLE in humans presents obvious inherent limitations. Cause–effect relationships between immune factors and behavioral outcomes cannot easily be characterized in such paradigm and diagnosis is often made after SLE is in late stages of progression. An approach allowing to characterize the early underlying mechanisms of NPSLE in a quite systematic and more direct way includes investigation based on murine models which, then, permits to study interactions between autoimmune/inflammatory processes and cerebral functions, and to better understand the cellular and genetic mechanisms of the disease [17,60,61].

3. Murine models of SLE

3.1. Presentation

Several animal models present immune complex-mediated glomerulonephritis associated with immunological abnormalities that are comparable to those reported in human SLE. Three families of murine models have been described, namely spontaneous, induced and genetically-engineered knockout and transgenic models (Table 2). In this review, we will focus our attention on one spontaneous model of lupus, the MRL-*lpr* mouse, in relation with cognitive dysfunction. Detailed information dealing with numerous other mouse models can be found elsewhere [17,18,62–66]. In the list of relevant murine strains, it is worth noting the

development of a model based on Abs cross-reacting with native, double-stranded (ds)DNA and *N*-methyl-D-aspartate (NMDA) glutamate receptor that shows cognitive impairment and emotional disturbances mediated by these autoAbs [67–70].

Generally, for modeling NP manifestations of lupus, spontaneous models are liked best. The most commonly studied spontaneous models have been made available by selective inbreeding and include BXS_B, the F1 hybrid between New Zealand Black (NZB) and New Zealand White (NZW) mice called (NZB/W)F1, and the Murphy Roths large (MRL) strain. Over varying periods of time, all these mice spontaneously exhibit clinical and serological features comparable to manifestations seen in human SLE [61]. The mice not only share features such as hypergammaglobulinemia, inflammatory lesions, B cell hyperactivity, autoAbs, circulating immune complexes, and glomerulonephritis [71], but also possess unique characteristics, such as monocytosis in BXS_B mice, hemolytic anemia in NZB mice, arthritis and expanded CD4⁺CD8[−] double negative T cells and rheumatoid factors (RF) in MRL-*lpr* mice. Differences in autoimmune disease manifestations are also noticed among strains concerning sex, age of onset, symptoms' severity, and rate of development.

3.2. The MRL-*lpr* mouse model

The MRL-*lpr* strain is one of the best established spontaneous models of SLE and the most extensively investigated in lupus-related NP studies. These mice develop an accelerated and aggressive lupus-like disease characterized by immune-mediated damage to the kidney, skin, heart, lungs, joints, and brain, and by the presence of circulating autoAbs against dsDNA and Smith antigen, which are serological hallmarks of SLE. It has been estimated from the breeding history of MRL mice that its composite genome is derived 75.0% from LG/J, 12.6% AKR/J, 12.1% C3H/HeDi and 0.3% C57BL/6J [72]. In the 12th generation of the MRL inbreeding, a spontaneous autosomal recessive mutation divided the stock (#00486) into two substrains, one with the so-called lymphoproliferation gene (*lpr*) and the other without, leading to two groups of mice, the MRL/MpJ-Fas^{*lpr*} (MRL-*lpr*; stock #00485) and the MRL/MpJ^{*lpr*}/Fas (MRL^{+/+}, stock #006825), with at least 89% (and more than 99.9% after several cycles of cross-intercross mating) of their genome in common.

Both congenic strains are comparable for several aspects (e.g. appearance, size, reproductive age) and develop autoimmunity accompanied by CNS involvement, although much slowly and later in life for MRL^{+/+} mice, thus representing a natural and adequate control [61]. Furthermore, MRL^{+/+} mice do not show evidence of CNS damage under normal conditions, unlike MRL-*lpr* mice which, as it will be discussed much further below, develop spontaneous BBB leakage. The main factor accounting for the accelerated autoimmunity in the

Table 2
Examples of some murine models of systemic lupus erythematosus.

Type of murine model	Murine model	Major autoimmune manifestations	NP manifestations
Spontaneous	MRL/MpJ-Fas ^{<i>lpr</i>} (MRL- <i>lpr</i>)	Glomerulonephritis; arthritis; vasculitis; skin lesions; alopecia; myocardial infarcts; autoAbs (including RF)	Emotional and cognitive dysfunctions: anxiety, depression, anhedonia, decreased locomotion, impaired spatial learning
	NZB; (NZB×NZW)F1	Glomerulonephritis; hemolytic anemia; pulmonary infiltrates, autoAbs	Impairment in learning and mood-related behaviors
	BXS _B	Glomerulonephritis; myocardial infarcts; monocytosis, autoAbs	Impairment in spatial abilities in old males
	Palmerston-North	Glomerulonephritis; polyarteritis nodosa; autoAbs	ND
	Motheaten	Mild glomerulonephritis; pulmonary infiltrates; hair loss; autoAbs	ND
Induced	Pristane-induced	Glomerulonephritis; autoAbs	ND
Genetically engineered	• Knockout		
	Apcs ^{−/−}	Glomerulonephritis; anti-chromatin Abs	ND
• Transgenic	Bcl-2 transgene	Glomerulonephritis; lymphoid hyperplasia; autoAbs; hyperIgG	ND

Abbreviations: Ab, antibody; Apcs, serum amyloid P component; Bcl-2, B-cell lymphoma 2 (B cell promoter); Fas, apoptosis stimulating fragment; F1, hybrid of the 1st generation; Ig, immunoglobulin; *lpr*, lymphoproliferation gene; MRL, Murphy Roths Large; ND, not determined; NP, neuropsychiatric; NZB, New Zealand Black; NZW, New Zealand White; RF, rheumatoid factors.

MRL-*lpr* substrain is a defect in the *Fas* gene expression, produced as related above by a spontaneous mutation of the single autosomal recessive gene *lpr* located on chromosome 19. This mutation alters transcription of the *FAS* receptor [73] and results in lymphadenopathy [74]. It also interferes with normal *FAS*-induced apoptosis, contributing to prolonged survival of activated lymphocytes and autoreactive T- and B-cell clones, and finally, in high autoAb titers [75]. MRL-*lpr* mice significantly differ from the other lupus models by the development in certain mice colonies of a rheumatoid arthritis-like polyarthritis, with a high incidence and titer of RF in their serum, and high levels of circulating immune complexes and cryoglobulins. It is important to know that over the past decade, MRL-*lpr* mice displayed “accidental” lessening of symptoms of unexplained origin [76] and that the MRL-*lpr* original stock was re-established in 2008 (<http://jaxmice.jax.org/strain/006825.html>). This event has been recounted in detail elsewhere [16,77].

MRL-*lpr* mice display an accelerated mortality rate, females dying approximately at 17 weeks of age and males at 22 weeks. Similarly to lupus patients, MRL-*lpr* mice spontaneously develop behavioral dysfunction concerning emotional reactivity, motivated behavior, cognition, as well as pathologic changes in the brain (i.e. degeneration of central neurons) [62,78–87]. Experimental studies showed that behavioral deficits parallel high levels of cytokines and autoAb, such as antinuclear Abs, anti-dsDNA, and RF, resulting in large amounts of immune complexes [71]. This model, as we will see below, has now become an indispensable tool in the attempt to elucidate the pathogenesis of NPSLE [16], and helped in revealing autoimmunity-induced degeneration, as well as the cytotoxic effects of IgG-rich CSF [79,88].

As in human SLE where depression and other kinds of NP manifestations can appear early in the time course of the disease [15,89], authors found that depressive-like behavior is exhibited by MRL-*lpr* mice (stock #006825) already at 8-weeks of age, at a time when there was no other apparent organ involvement [90]. Thus, these mice demonstrate increased immobility in the forced-swim test, which is usually accepted as an indicator of depression in rodents if strength, motor coordination and general locomotion are otherwise normal (mice's motor function had been evaluated and revealed no impairment in the beam-walking as well as in open field tests). Depressive symptoms significantly correlated with titers of autoAbs against dsDNA, NMDA receptor and cardiolipin. This observation indicates that lupus mice develop depression and CNS dysfunction early in the course of the disease, in the absence of substantial pathology of other organs. This observation also confirms, in the MRL-*lpr* model, the robustness of emotional dysfunction by providing further evidence that such behavioral outcomes are likely a primary manifestation of autoimmunity rather than arising from nonspecific illness or peripheral organ pathology. Finally, MRL-*lpr* mice also display anhedonia, another manifestation of murine depressive-like behavior [91], which is a lack of response to pleasure or reward and is assessed experimentally in following the loss of the typical preference to drink sweetened fluids [92]. Anhedonia is classically considered as a hallmark diagnostic symptom of depression and, in this report, it correlates significantly with a depression-like phenotype in the forced-swim test.

An interesting finding in MRL-*lpr* mice concerns the sex bias of the disease. In human SLE, a strong gender preference (about a 9:1 female to male ratio) is generally found [93]. Recently, authors evaluated MRL-*lpr* mice, by directly comparing males and females (stock #00485) [94], and found that MRL-*lpr* females from this stock exhibited depression as early as 5 weeks as compared to MRL-*lpr* males where depression was noted only at 18 weeks. Depression scores significantly correlated with autoAbs against nuclear antigens, NMDA receptor, and ribosomal P proteins. These results are consistent with the notion of a primary role of autoAbs in the pathogenesis of early NP deficits in this lupus model, which translate into gender-based differences in clinical phenotype. In human SLE and murine MRL-*lpr* model, a different hormonal component can influence the disease progression between both sexes. Additionally, higher levels of IgG can be found in CSF of female MRL-*lpr* mice [95].

Subtle differences in the susceptibility of the male and female MRL-*lpr* brains to injury by pathogenic Abs may then lead to a more severe neuro-behavioral phenotype in female lupus mice.

4. Neurobehavioral testing in MRL-*lpr* mice

As many patients with SLE, evidence suggests that MRL-*lpr* mice show changes in emotional function and cognition [82,96] in parallel with, but sometimes also before, abnormalities in the immune system. Mainly, anxiety and depressive-like behaviors have been observed [97]. This finding has raised the possibility that the characterization of behavioral modifications in autoimmune mice may help clarifying the link between autoimmunity and cognition. To examine the time course of behavioral outcomes of lupus (i.e. anxiety, feelings of helplessness or despair, anhedonia commonly described by NPSLE patients), the performances of mice, including anxiety-like behavior, depression or sickness-like behavior, cognition, as well as locomotor activity can be evaluated in a battery of tests, which are detailed below.

4.1. Anxiety tests

4.1.1. Elevated-plus maze

This maze is routinely used in pharmacology due to its sensitivity to anxiolytics. It consists of four arms, two enclosed and two open (i.e. without walls), and creates an approach-avoidance conflict between the natural tendency of rodents to explore and their aversion for open spaces (which helps preventing detection from predators). In such test, anxiety-like behavior is typically defined as the decreased exploration of open arms; the more anxious the animal is, the less it will explore them [98]. Concerning the MRL-*lpr* model, some authors reported increased anxiety levels [82] while others failed to find such effects [90,94,99].

4.1.2. Open field

This test assesses exploratory behavior in a novel, enclosed environment, which can also reflect anxiety-like behavior, as measured by the amount of time the animal avoids the central area of the arena and remains in close proximity to the walls (thigmotaxis) [100]. The degree of stress can be experimentally manipulated (i.e. by increasing enclosure's size, changing its color—white is more stressful than black—varying the intensity of the overhead lights). In this experimental situation, MRL-*lpr* mice display anxiety-like behavior as evidenced by increased thigmotaxis and impaired exploration of space [82].

4.2. Depressive, sickness-like behavior tests

4.2.1. Sucrose preference test

Reduced preference for palatable drinking solutions was first noted in one of the pioneering studies on behavior of MRL-*lpr* mice [101]. This observation was further explored using the sucrose preference paradigm summarized above. In the MRL model, this paradigm reveals impairments in motivated and goal-directed behavior, and no changes in peripheral sensory input [102]. It is noted as early as 5–6 weeks of age in female mice [103] and continues during the active disease phase (4–5 months) [104–106].

4.2.2. Forced-swim test

This test evaluates behavioral despair as the proportion of immobility when rodent is placed into a small container of room-temperature water from which escape is impossible. After a period of struggling and swimming, the animal becomes immobile, moving its limbs only when it needs to stay afloat or to rebalance itself. This immobility has been interpreted to reflect a state of “behavioral despair” or helplessness, which occurs when the animal learns that escape is impossible [107,108]. Within this interpretation, immobility is thought to reflect a depressive-like behavior and is illustrated as the percentage of time

spent immobile [109]. Increased floating is one of the most profound performance deficits observed in MRL-*lpr* mice, appearing as early as 5 weeks of age and persisting throughout the course of the disease [82,83,90,94]. However, it is equally possible that immobility is an adaptive response that allows the animal to keep its energy. Thus, it remains debatable whether the forced-swim test can be considered as a test of depression.

4.2.3. Open field locomotor activity

Further symptoms of depressive-like behavior include fatigue and apathy which can be assessed as both decreased voluntary activity and exploration in a novel environment, such as an open field. Generally, MRL-*lpr* mice are spontaneously less active [80,82,94,110].

4.3. Cognition: learning and memory tests

Parallels exist between forms of memory assessed in rodents and those evaluated in humans, all being related to hippocampal processes.

4.3.1. Novel object recognition (visual memory)

This test is based on the robust tendency of rodents to preferentially explore novel objects. It is efficient to assess non-spatial working memory, but it also reflects explorative and emotional responses in an approach-avoidance situation, where MRL-*lpr* mice usually display deficits [82,111]. The mouse is first placed into an arena containing two identical, novel objects. After a predetermined period of exploration, the animal is removed, and a delay is imposed. Following the delay, the mouse is placed back into the arena, where one of the objects is replaced by a novel object. Rodents typically explore novel objects and avoid familiar objects, so the amount of time investigating the novel object is taken as the measure of working memory. Generally, MRL-*lpr* mice are not impaired in this cognitive component of the task [90,94].

4.3.2. Morris water maze

This test assesses spatial learning and memory formation. Animals are placed into a pool of water in which a platform is hidden beneath the surface. The animal must learn to use spatial cues located in the testing room to navigate to the platform. Longer latencies indicate poorer performance. MRL-*lpr* mice present significant deficits in this test; they are dramatically impaired in their ability to learn the spatial relationships required to guide them to the hidden platform [80,81,86,112].

4.3.3. Fear-conditioning paradigm

The fear conditioning test assesses the ability of an animal to associate a conditioned stimulus (CS, neutral) with delivery of an unconditioned stimulus (aversive), usually foot-shock. Several dependent measures can be employed, although the most simple is to assess the degree of freezing that the CS elicits. The CS can be either contextual (the arena in which shock is administered), or it can be discrete (a light or tone cue that precedes the shock). Variations in the type of CS recruit neuroanatomically distinct systems; the hippocampus has been found to be crucial to supporting cued fear conditioning with a discrete CS, whereas the amygdala is essential to the acquisition and expression of contextual fear conditioning. This experimental paradigm has been used by Diamond and her group in another murine lupus model based on Abs cross-reacting with dsDNA and NMDA receptors. These authors reported disruption of emotional behavior as a consequence of a neuronal loss in the lateral amygdala [68].

4.4. Motor function tests

4.4.1. Beam-walking test

Walking on a narrow beam (diameter of 1.5 cm) is often used to test psychomotor coordination [113] and is sensitive to motor cortex damage. Motor coordination is assessed as the latency to cross the beam (100 cm-long) and the number of slips (i.e. when one of the paws is

passing below the midline of the beam). Generally, there is no obvious deficit, MRL-*lpr* mice displaying normal motor coordination [90,94].

4.4.2. Climbing test

The test consists of placing mice in a wire-mesh rectangular box over 10 min; duration and frequency of climbs, rears and grooming episodes are scored. Spontaneous climbing is a behavioral pattern proposed to be controlled by the dopamine system [114]. There is evidence suggesting aberrant dopaminergic neurotransmission in MRL-*lpr* mice [83,104,105].

5. Why are MRL-*lpr* mice a good model for NPSLE?

5.1. Disruption of the BBB

The BBB, composed of a network of endothelial cells, pericytes and astrocytes, is a crucial anatomic location in the brain. It functions to limit the entry of soluble molecules and cells into the brain parenchyma, and to maintain a regulated micro-environment for reliable neuronal signaling in the CNS [115]. As mentioned above, evidence for BBB breakage or leakage in human SLE-related neuropathology is now accumulating [37–39,41]. Similarly to NPSLE patients, MRL-*lpr* mice show increased albumin concentration and IgG index, which, interestingly, are concomitant with neurodegeneration in periventricular areas [95]. Recently, experimental findings (i.e. IgG infiltration into brain parenchyma) even account for a definite loss of BBB integrity in this lupus-prone model [116]. Finally, using immunohistochemical markers and flow cytometry to assess distribution and prevalence of various cell subtypes, including plasma cells, which infiltrate the brain of MRL-*lpr* mice, other authors observed a massive penetration of CD3⁺ T cells into the choroid plexus and brain parenchyma, as well as the presence of CD19⁺ cells and CD19⁺IgM⁺ B cells, which increased in the brain. Severe mononuclear cell infiltration was accompanied by splenomegaly and retarded brain growth [117]. These data support the hypothesis of progressive neurodegeneration as a consequence of leukocyte infiltration and intrathecal autoAb synthesis. However, challenging questions remain as to determine when and how a loss of the BBB integrity can occur.

5.2. Evidence of pathogenic Abs

The hypothesis of a pathogenic role of certain brain-reactive Abs in mental disorders [31,118] is strengthened in MRL-*lpr* mice where analysis of serum repeatedly showed increased levels of autoAbs, noticeable earlier in females and paralleling the onset of depressive-like behavior [90,94].

After a disruption of BBB, autoreactive Abs can penetrate into the brain where they may cause neuronal death [69] and eventually psychosis and/or seizures in lupus patients [119]. In addition to be detected in the CSF following BBB break, autoreactive Abs might also be produced intrathecally [40,120,121]. Experimental studies support this last hypothesis in MRL-*lpr* model [79]. Intrathecally-generated Abs are of the IgG isotype [95] and their levels correlate with increased immobility in the forced-swim test [122]. These authors proposed that intrathecal brain-reactive Abs predict depressive-like response while anxiety-like behavior and “anhedonic” response are rather associated with circulating Abs [111].

The general observation that behavioral abnormalities appear before major increase of serum Abs titers or detectable BBB disruption indicates that serum Abs are not the unique pathogenic factor on NPSLE, at least early in the disease. The link between serum and CSF autoAbs to the disease process is complex and evidences suggest that CSF Abs are more pathogenic than serum Abs [43,79,123,124].

5.3. Cytokines

The neuromodulator role of cytokines is highly relevant in diseases characterized by inflammation, such as lupus, in which proinflammatory cytokines are involved in the pathogenesis of tissue injury and in the production of pathogenic autoAbs [125]. Cytokines play a central role in cognitive function, as well as in learning and memory in the hippocampus [126]. They have been linked to depression in humans [127] and a dysregulation of certain proinflammatory cytokines is thought to be involved in the CNS manifestations of SLE [128–130].

Cytokines affecting the brain may originate either peripherally or centrally [131]. Resident CNS cells, neurons, astrocytes, and microglia cells constitutively produce and express receptors for most of the cytokines produced in the periphery. On the other hand, cytokines are produced within the CNS by neurons and microglia, the surveillance cells of the CNS (for a review, see [132]), and take part in the regulation of neurogenesis, cell survival, proliferation and differentiation of new neurons that is crucial for hippocampal functions such as learning and memory [133,134].

In MRL-*lpr* mice, increased serum levels of proinflammatory cytokines, including tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6, parallel the progress of lupus-like disease [135–137]. As well, they are known to alter emotional reactivity and motivated behavior, to provoke sickness behavior clinically and induce impairments in spatial learning experimentally [103,138–142]. To explore the relationships between cytokines and CNS disease in lupus, the expression of several proinflammatory cytokine genes in the hippocampus of autoimmune MRL-*lpr* mice was compared [143,144]. The results indicate that the proinflammatory cytokine genes for interferon (IFN)- γ , IL-1, IL-6 and IL-10, which have been shown to induce cognitive and emotional impairments, are selectively up-regulated in the hippocampi of MRL-*lpr* mice. Thus, proinflammatory cytokines may play a role in the cognitive aberrations observed in MRL-*lpr* mice and, by extension, in lupus [145]. Finally, increased expression of TNF and of its receptor TNFR1, which are moreover implicated in induction of inflammation and degeneration/apoptosis in the CNS, had been reported in the brain of MRL-*lpr* mice [146].

5.4. Neuroinflammation–neurodegeneration

Neuroinflammation and neurodegeneration represent important components of NPSLE. In MRL-*lpr* mice, the brain metabolism is dramatically altered [147], and the early onset of inflammation and autoimmunity includes pathologic events such as infiltration of mononuclear cells into the choroid plexus and parenchyma [87,112,148], increase of adhesion molecules [149], as well as deposition of complement proteins.

In MRL-*lpr* mice, the possibility of congenital brain structural defect potentially confounding disease-induced neurodegeneration is minimized as these mice do not show such inherited cerebral abnormalities, in contrast to BXSB and (NZB \times NZW)F1 [150,151]. Then, the MRL model allows the study of interrelationships between systemic autoimmunity, brain changes, and behavior outcomes in a quite controlled way. From a developmental point of view, brain growth appears retarded [152] and ventricles increase in size along an early and accelerated development or autoimmune manifestations [153,154]. Furthermore, and particularly in the hippocampus (i.e. cerebral subregion crucially involved in cognitive processing), increased neurodegeneration, reduced dendritic complexity and progressive atrophy of pyramidal neurons have been commonly observed [88,155], accompany deficits in spatial learning memory [96,152], and are also consistent with the notion of an anxious/depressive-like behavioral profile [82,106,156]. Interestingly, hippocampal abnormalities also exist in human lupus [157–159]. Moreover, reports concerning reduced brain weight [84,152], and neurotoxicity of CSF [79] reinforce the notion of neuronal damage in the MRL-*lpr* substrain. Finally, in MRL-*lpr* mice, lesions of the nucleus accumbens accompany impaired motivated behavior (sucrose preference test) [104],

and degeneration in the *substantia nigra* is reported with decreased locomotor activity [105]. Taken together, these data support the notion that systemic inflammation and autoimmunity induce structural damage and degeneration of central neurons (e.g. hippocampal), thus likely forming the basis of behavioral deficits in MRL-*lpr* substrain.

Progenitor cells may also degenerate in the brain of MRL-*lpr* mice. Thus, cerebral regions (e.g. subventricular zone, subgranular zone of the hippocampus) containing such progenitor cells [160] show signs of neurodegeneration [95,96,155,161]. Concerning neuronal progenitor cells, authors report that CSF from MRL-*lpr* mice, as from a deceased NPSLE patient with a history of psychosis, memory impairment, and seizures, are toxic and reduce the viability of brain cells, which proliferate in vitro (C17.2 neural stem cell line) [123]. This harmful effect was accompanied by periventricular neurodegeneration in the brain of autoimmune mice and in vivo neurotoxicity when their CSF was administered to the CNS of a rat. Proposed mechanisms of cytotoxicity involve binding of intrathecally synthesized IgG autoAbs to target(s) common to different mammalian species and neuronal populations. These results indicate also that the viability of proliferative neural cells can be compromised in systemic autoimmune diseases. Then, Ab-mediated damage of germinal layers may weaken the regenerative capacity of the brain in NPSLE, as well as in cerebral development and function in other CNS diseases in which autoimmunity has been documented [162]. Interestingly, impaired hippocampal neurogenesis could account for some of the cognitive deficits observed in MRL-*lpr* mice, as the hippocampus is well implicated in learning and memory processes [163]. Finally, hippocampal neurogenesis could also be inhibited by stress hormones, which are chronically increased in MRL-*lpr* mice [164].

Impaired neurotransmitters (i.e. dopamine, serotonin, norepinephrine, glutamate) catabolism could also be involved in the pathogenesis of CNS damage in lupus. This hypothesis was studied in MRL-*lpr* strain by evaluating the neurotransmitter/metabolite levels in several brain regions [104,105,165]. MRL-*lpr* brains showed increased dopamine levels in the paraventricular nucleus (PVN) and the median eminence, decreased serotonin concentrations in the PVN and enhanced levels in the hippocampus, and decreased norepinephrine levels in the prefrontal cortex [83]. Behavioral deficits correlated with the changes in PVN and median eminence. Concerning serotonin, data are in line with modified serotonin levels in SLE patients comparable to what occurs in depressed patients, including those in which depression has been induced by cytokine therapy [166]. Taken together, and more generally, these results are consistent with the notion that imbalanced neurotransmitter regulation of the hypothalamus–pituitary–adrenal (HPA) axis may play a significant role in the etiology of behavioral dysfunction induced by systemic autoimmune disease [83], and may induce neurotoxicity, at least for dopamine [167]. A deficit in this neurotransmitter release, moreover, may underlie impaired responsiveness to palatable stimulation during the progress of systemic autoimmune disease [104]. As such, a neurotransmitter-specific regional brain damage may account for depressive behaviors in NPSLE.

5.5. Neuroendocrine-immune interaction

The interaction between the nervous, endocrine and immune systems remains poorly understood. The HPA axis is the chief component of the stress system. The stress-induced increase serum concentration of glucocorticoids is essential for the prevention of autoreactive or uncontrolled amplification of the immune response, which results in autoimmunity and self-injury. A defective HPA axis may then confer susceptibility to autoimmune disorders, and it seems that such a deficiency is present in both murine and human lupus [110,164,168]. Nowadays, studies on the function of the HPA axis are rather limited in patients with SLE and often confounded by the effect of concomitant glucocorticoid treatment. Nevertheless, it is well documented that proinflammatory cytokines modulate the stress hormone system and alter behavior [169–171]. Such cytokines activate the HPA axis via

corticotrophin-releasing hormone, stimulating the synthesis of glucocorticoids and other neuropeptides [172,173]. In MRL-*lpr* mice, increased levels of proinflammatory cytokines, mimicking actions of glucocorticoids on the HPA axis, accompany the spontaneous onset of SLE and are associated with deficits in learning and memory function, resulting from hippocampal atrophy. Elevated cortisol levels could also cause excitatory amino acid injury to neurons via a direct decrease in synaptic reuptake of glutamate. The notion of glutamate toxicity is supported by the evidence of anti-NMDA receptor Abs resulting in neuronal apoptosis in the mouse brain [67], and a similar IgG-mediated mechanism induced by CSF from MRL-*lpr* mice [123].

Concerning the time course and the nature of CNS involvement, a report focusing on the neuroendocrine-immune characteristics of MRL-*lpr* mice recently showed that behavioral deficits are under the control of autoimmune, genetic, and endocrine factors, which interchangeably affect brain function and morphology at different phases of ontogeny [174]. Thereby, behavioral performances during the prodromal phase of NPSLE-like disease are associated with autoAbs in CSF and asymmetric activation of the HPA axis. Subsequent deterioration in behavior evolves alongside systemic autoimmunity and inflammation. Although a leaky blood-CSF barrier is a possible explanation, the authors hypothesized that, similar to neonatal lupus, maternal Abs to brain antigens might cross blood-placental barrier during embryogenesis and induce early endocrine and behavioral deficits in offspring.

The different interactions, which seem to exist in MRL-*lpr* mice between genetic, nervous, endocrine, and immune systems, and may induce abnormalities in cognitive behavior, are depicted in Fig. 1.

5.6. The MRL-*lpr* mouse model to evaluate potential neuroprotective drugs

We recently showed that in MRL-*lpr* mice, the cGMP-phosphodiesterase (PDE) activities are significantly increased in the kidney, spleen and liver. PDE1 activity levels were raised in their kidneys (associated with nephromegaly) and liver, and PDE2 activity was specially increased in their spleen [175]. Nearly all the PDE families are expressed in the CNS [176]. In our hands, the basal expression levels of PDE1, 2 and 5 measured in the brain of 15 week-old MRL-*lpr* mice were not significantly changed (not published). Regarding the brain cAMP-PDE activity, however, while the basal activity also appeared unchanged, that of PDE3 was found to be significantly raised (62.5 to 165.7 pmol/min/mg; $p = 0.0017$, Student's test; results obtained in three female mice of 15 weeks of age; Lugnier and Keravis, personal communication; Fig. 2). It is worth mentioning that a single intravenous administration to MRL-*lpr* mice of nimodipine (PDE1 inhibitor) but not

of EHNA (PDE2 inhibitor) was able to significantly lower peripheral hypercellularity [175], which is a typical feature of this strain of lupus mice (see above). It remains to be explored if drugs known to inhibit cAMP-PDE3 activity are able to display such an effect and possibly reverse some neurological signs observed in this mouse model.

6. Limitations

Although the MRL-*lpr* strain displays many features reminding human NPSLE, there are some limitations which must be taken into account when studying NP features in this murine model.

First, several differences exist between human and rodent immune systems. Since autoimmune dysfunctions are at the root of autoimmune diseases, such particularities may limit extrapolations from animal models to autoimmune patients and precautions have to be taken for interpretations and conclusions of what it has been observed experimentally.

Thus, in contrast to the oscillating course of flares and remissions commonly reported in SLE patients, MRL-*lpr* mice show a constant disease progression [18,60], which likely reflects the fact that these mice are genetically-altered for some genes, such as *fas*, on a predisposing MRL background. We must remind here that if *FAS* mutations result in a familial autoimmune lymphoproliferative syndrome, defects in *FasL* have scarcely been found in lupus patients. *FAS* and *FASL* are not considered contributory genes in human SLE.

Furthermore, while affective and cognitive states of NPSLE patients can be measured by quite sophisticated tests, performances of MRL-*lpr* mice can only be evaluated using a battery of behavioral tests. Care is then required when transferring information observed in MRL-*lpr* mice to human SLE patients.

Finally, as in any reductionist approach, this murine model provides presumably a partial view only of the complex mechanisms occurring in human disease. Nonetheless, animal models are at the core of autoimmune research and numerous published studies reflect the progress brought by these animal models in terms of depicting disease mechanisms.

7. Conclusions

Clinically, NP involvement in several diseases is closely associated with, and is thought to be a consequence of, inflammation in the brain. Several studies report specific autoimmune responses to self-antigens in psychosis, affective dysregulation, and other behavioral abnormalities. Nowadays however, despite these data, no autoAbs have

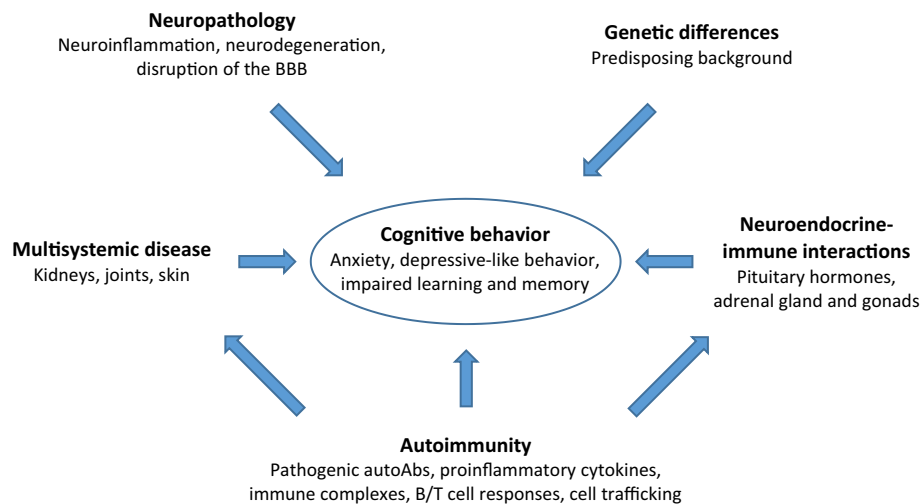


Fig. 1. Potential factors influencing cognitive behavior and abnormalities in MRL-*lpr* mice. The involvement and relative contribution of each factor may vary during different stages in the development of autoimmune disease. Abbreviations: Abs, antibodies; BBB, blood-brain barrier; MRL, Murphy Roths Large.

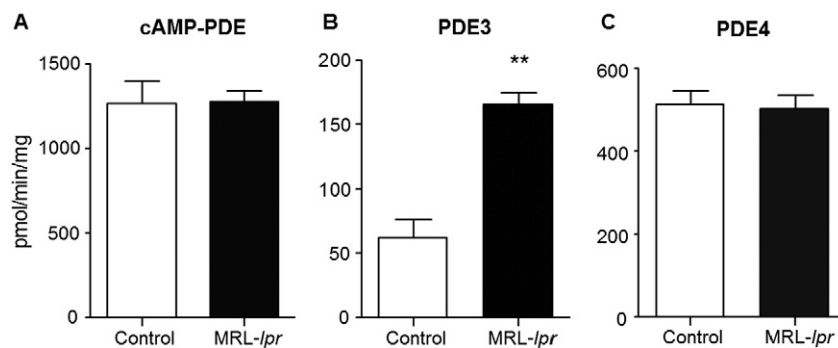


Fig. 2. Levels of basal cAMP-PDE activities in the brain of normal and lupus mice. Basal cAMP-PDE specific activities in total homogenate (A) and contribution of PDE3 (B) and PDE4 (C) were assessed on 15 week-old CBA/J and MRL-*lpr* mice as described by Yougaré and collaborators [175]. Data are expressed as pmol/min/mg of protein and are the mean \pm s.e.m. of the data obtained from three individual mice. **, $p < 0.01$ (Student's test) (Lugnier and Keravis, personal communication). All experimental protocols were carried out with the approval of the local Institutional Animal Care and Use Committee (CREMEAS). Abbreviations: cAMP, cyclic adenosine monophosphate; CBA/J, C.C.x Bagg, strain A/Jackson; MRL, Murphy Roths Large; PDE, phosphodiesterase.

remained sufficiently reproducible or ubiquitous as to become a robust biomarker for disease. Experimentally, there is considerable evidence to indicate that chronic inflammation may lead to neurodegenerative disorders [177].

The MRL-*lpr* model presents several advantages as compared to other models of systemic autoimmune disease that render it an indispensable tool in studies of autoimmunity-brain interactions. Spontaneously, these mice present cerebral neuroanatomic and neurobehavioral changes similar to what is observed in human lupus, thereby indicating the validity of their use to investigate the mechanisms underlying neurobehavioral dysfunction in human SLE. An age-dependent decline in brain mass and hippocampal size are consistent with a cascade of pathogenic events, including CSF-mediated cytotoxicity, neurodegeneration and impaired neurogenesis in the limbic system, which accounts for early changes in emotional reactivity and cognitive dysfunction. Moreover, the MRL-*lpr* model is heavily relied upon because of its wide spread availability (it is commercially available), ease of use, and has disease occurring in a compressed time.

Research is still at the beginning concerning knowledge of how frequently Abs cause brain damage, which are their mechanisms of gaining access to the brain, how they potentially affect cerebral functions, and/or if other effector molecules can also display deleterious effects [178]. These questions are central in our quest to generate adapted therapeutics capable of specifically hampering the binding of brain-reactive Abs or active molecules to their targets. In this setting, availability of pertinent animal models mimicking NPSLE is crucial to elucidate precise disease factors and molecular events occurring during neuronal cell death and then to evaluate such therapeutic tools designed on the basis of acquired information.

Take-home messages

- NP symptoms of SLE (NPSLE) are dramatic complications of the disease and contribute to significant morbidity and mortality.
- Animal models are useful tools in defining the pathogenesis of human disease.
- The MRL-*lpr* strain is a murine model of lupus, which spontaneously develops specific serological (e.g., autoAbs, proinflammatory cytokines) and behavioral features (e.g. cognitive, emotional dysfunction) of human SLE.
- There is a link between autoimmune/inflammatory disease, neurodegeneration and behavioral dysfunction in MRL-*lpr* mice.
- The MRL-*lpr* substrain may constitute an excellent model to evaluate neuroprotective therapeutics.

Conflict of interest

Both authors declare no financial conflict of interest.

Author contribution

Both authors contributed in writing the article.

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